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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,332	02/15/2002	Yuji Ishihara	2599 USOP	5909

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EXAMINER
CHANG, CELIA C

ART UNIT	PAPER NUMBER
1625	11

DATE MAILED: 04/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,332	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *25 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-24,26-28 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 & 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group I, claim 14 in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the reason for traversal or the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

With respect to claims 25 and 29 as requested by applicants, it is regretted that an oversight of conveying to applicants that these two claims are withdrawn from consideration because they are drawn to the nonstatutory "use" format which are improper under 35 USC 101 (see MPEP 2713.05(q)).

Claims 14 and generic claims 1-13, 15-21, 26-28, 30-39 reading on R1-R2 is an optionally substituted piperidine is examined. The remaining subject matter and claims 25 and 29 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "hydrocarbon optionally having a substituent or substituents" is ambiguous and confusing. Please note that the definition of hydrocarbon is composed of hydrogen and carbon. Therefore, when a nonhydrocarbon substituents is attached to the moiety is such a compound within the scope or not? It is recommended the specific linker be specifically pointed out with the optionally substitutions particularly incorporated for such elements.

3. Claims 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is self-conflicting since it is a pharmaceutical composition but without any quantitative limitation. Please note that a pharmaceutical composition cannot be either

ineffective or toxic, therefore, must have a therapeutically effective amount of the active ingredients.

Claims 17-24 are ambiguous and confusing because it is a pharmaceutical composition containing an "agent" "antagonist" or a "protease inhibitor" or "reverse transcriptase inhibitor". Please note that it is confusing whether the "agent" etc. is a quantitative limitation of an active compound or is it only when the composition is being used for protease inhibition etc. Please note that the claims are in product/use hybrid format thus are unclear of its meets and bounds. Further, the combination compositions without specifics included those protease inhibitor, reverse transcriptase inhibitor etc. which are not yet known for which description and enablement are lacking from the specification (a 112 first paragraph rejection will follow). It is recommended that if the claims are drawn to composition the particular dosage based on efficacy i.e. "a CCR5 chemokine receptor antagonistic effective amount of a compound.... " etc. be incorporated.

4. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for prodrugs in form of pharmaceutically acceptable acid/base addition salt or N-acylated prodrug conventionally known, does not reasonably provide enablement for "any and all" prodrugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Please note that the term "prodrug" encompassed such modifications such as target specific carrier, taste masking etc. (see Silverman) for which description and enablement are lacking from the specification.

5. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of HIV in spreading to uninfected cells, does not reasonably provide enablement for the scope of the instant claim as suppressing all chemokine receptor activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to operate the invention commensurate in scope with these claims.

Please note that the instant compounds being CCR5 chemokine receptor inhibitory does not offer any descriptive or enabling support for all chemokine receptor activity. It is well known in the art that chemokine receptor function is complexed and highly unpredictable (see Cohen et al. CA 125). While specific chemokine can link to a specific biological reaction, the mechanisms of chemokine (which is a kind of cytokine) function is very limited.

Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for composition comprising specific combinations of two active ingredients disclosed on page 38, does not reasonably provide enablement for the claimed scope encompassing any and all combination of the compounds with protease inhibitor, reverse transcriptase inhibitor with multiple active ingredients and including those protease inhibitor or reverse transcriptase inhibitor which have not yet be discovered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Please note that not only the utility in treating diseases with such broad spectrum by the claimed compounds is unpredictably as evidenced supra, the combination of biological active ingredients are highly unpredictable especially in such pioneer field of combining new and unknown compounds. It is recommended that the claims be limited to the known and described combination disclosed on page 38, lines 24-34.

6. In so far as the elected compounds are concerned, claims 31-39 are essential duplicate of claims 4-12 i.e. when the nonelected compounds are deleted from claims 4-12 they are identical to claims 31-39. Essential duplicate claims are subject to double patenting rejection when one set of the claims become allowable (MPEP 706.03(k)). Cancellation of one set is recommended.

7. The following 103(a) rejections are made with the notice that the instant application claims priority benefit of PCT/JP00/0276 which claims priority benefit of JP11-122549. Since certified translation of the priority documents have not been provided the claimed priority benefit cannot be granted at this time. Therefore, the Kato reference constitute a 102(a) reference and the Kim reference constitutes a 102(e) or (g) reference.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(A)

Claims 1-13, 15-16, 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. CA 134.

Determination of the scope and content of the prior art (MPEP §2141.01)

Kato et al. disclosed a homologous species of the claims to have melanin concentrating hormone antagonistic activity.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Kato et al. disclosed all the elements of the claims **except** a species wherein R^2 is methyl for compound # 331756-17-3 was not exemplified. In the attached relevant pages, Kato generically taught that N-methyl is an optional choice for melanin concentrating hormone antagonist compounds as disclosed (see p.201 of 331756-17-3 and p. 281 example 202 N-methylated example).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the instant N-methylated compounds of Kato prima facie obvious because not only the one methylated homologs are considered prima facie obvious (In re Doebel 174 USPQ 158) in the chemical compound art, it is explicitly guided by Kato's generic teaching together with example 202. One skilled in the art would be motivated to prepared all the compounds generically taught by Kato and there is nothing unobvious in picking some among many (In re Lemin 141 USPQ 814) exemplified compounds with desirable attributes guiding one how to pick and choose among the genus for its known utility.

(B)

Claims 1-16, 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weber et al. US 4,891,378 in view of Chepkova and Patani.

Determination of the scope and content of the prior art (MPEP §2141.01)

Weber et al. '378 disclosed nootropic compounds and compositions having similar structure of the claimed compounds and the pyrrolidinone-piperidine examples are found at col. 11-12 table 1, 2nd and 6th compounds, and optional substitution being 4-benzyl found in 4th compound.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Weber et al. '378 are structural analogous compounds of the claims in that the difference between the two species and the instant claims is that the amido-N was not substituted and the linking chain has a CH_2NR^3CO instead of $CONR^3CH_2$.

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the Weber compounds prima facie obvious over the claims **because** the N-alkylation is generically taught and exemplified among the examples of compounds in table 1 (see col. 9-10 compound 8-9) and Weber 's compounds are peptide mimic nootropic compounds (see Chepkova et al. CA 114) thus, in analogous art it was taught the peptide mimic linker would be an optional choices of modification for such compounds especially Patani et al. taught that such peptide/amide bond modification is known as the bioisoterism which is a rational approach in drug design. Thus one skilled in the art in possession of Weber, Chepkova and Patani would be suggested by the references that the linker modification would be successful and having similar activity (Chepkova see 100462-32-6 with activity).

(C)

Claims 1-13, 15-24, 26-28, 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US 6,511,994 in view of Caldwell et al. US 6,136,827.

Determination of the scope and content of the prior art (MPEP §2141.01)

Kim et al. '994 disclosed compounds and compositions (col. 3 formula I, col. 27-32) encompassed the instant claims and a structurally very close species is disclosed at col. 98, line 55, example 42.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Generically, Kim et al. '994 disclosed all the elements of the claims **except** a species anticipating the claims was no exemplified while example 42 at col. 98, line 55 is a homolog of the claims wherein R^3 is H instead of the claimed methyl.

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the instant claims which are N-methylated compounds of Kim '994 prima facie obvious because not only the one methylated homologs are considered prima facie structurally obvious (In re Doebel 174 USPQ 158) in the chemical compound art, it is taught by Kim '944 in the generic teaching. Further, in analogous art by Caldwell et al. '827 which taught similar piperidinyl CCR5 compounds, it was explicitly taught that N-methylation of an amido linker in such compounds is a desirable attributes for such compounds (see col. 22-23 amido compounds) **because** among all the compounds disclosed by Caldwell '827 (see col. 16-61), all amido or sulfonamido "N" is substituted by an alkyl. Such exclusive disclosure is suggestion to one skilled in the art that such attribute is desirable and would be successful in analogous compounds (In re Baird 29 USPQ2d 1550). Therefore one skilled in the art in possession of Kim '994 with example 42 have been provided with the suggestive guidance from Caldwell '827 to the picking and choosing of the methyl homolog among the generic R^2 of Kim et al.'994 to modify the unsubstituted species of Kim example 42.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 703-308-4702. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner can be reached by facsimile at (703) 308-7922 with courtesy voice message supra.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Celia Chang
Primary Examiner
Art Unit 1625

OACS/Chang
April 14, 2003